REMARKS

This responds to the Office Action mailed on February 3, 2009.

Claims 173 and 200 are amended; claims 173-177, 179-194, 196-200, 202-203, , 205-206, 231, and 234 are now pending in this application.

The 35 U.S.C. § 102 Rejection

Claims 173-175, 177, 179-181, 196-200, 203, and 205-206 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ito et al. (WO 94/09764) evidenced by Schilling (Immunvaskulitis Therapiewoche, 25:1157 (1975)). This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

Ito et al. disclose the use of toremifene in mice to treat autoimmune diseases. In particular, it is disclosed that the administration of 100 mg/kg toremifene orally every day for 13 weeks to female mice with spontaneous autoimmune disease inhibited the appearance of autoreactive T cells (page 8).

Ito et al. do not teach or suggest locally administering a cytostatic dose of a compound of formula (I) to a human identified as being at risk of or having a cardiovascular or vascular indication characterized by a decreased lumen diameter or selecting an agent that is structural analog of tamoxifen or a pharmaceutically acceptable salt thereof that directly or indirectly elevates the level of active TGF-beta1 in a human and administering to a human identified as being afflicted with a cardiovascular indication an effective amount of the agent.

Therefore, withdrawal of the § 102(b) rejection is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 173-175, 177, 179-181, 196-200, 203, 205-206 and 231 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 (1992)). Claims 176, 182, 192, 194, 202, and 205-206 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ito et al. Claims 173-177, 179-194, 196-199, and 205-206 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang (U.S. Patent No. 5,445,941), and

claims 231 and 234 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang in view of Frank (Ophthalmology, 98:586 (1991)). These rejections are respectfully traversed.

Sawada et al. disclose that in order to evaluate the safety of toremifene, which is expected to be used in the treatment of breast cancer, toremifene was orally administered to female rats (pages 1 and 3 of the translation) for 52 weeks. In particular, it is noted that "[b]ecause the use of this drug is to be limited to female patients, only female rats were tested" (page 1 of translation). It is disclosed that the animals were divided into a control group and groups administered 0.01, 0.1, 1 and 10 mg/kg toremifene per day, and that the administered dose was 5 ml/mg. These amounts were based on earlier studies where a 0.7 mg/ml group showed toxic changes, including suppressed weight gain and total cholesterol reduction. Specifically, in concluding, Sawada et al. state that when toremifene was administered to female rats, "toxic changes were observed in the female reproductive system, pituitary, liver function and body weight" (page 12 of translation).

Thus, Sawada et al. teach that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. Sawada et al. also link decreased cholesterol to a change in liver function, which, in the case of tamoxifen, can be associated with liver tumor formation. See Sawada et al. at page 13. Sawada et al. is therefore teaching against the use of such dosages, due to the associated toxicity. In addition, Sawada et al. fail to teach, suggest, or imply that toremifene is or could be a therapeutic anti-cholesterol agent. In particular, Sawada et al. measured total cholesterol levels in the rats, which does not distinguish between a reduction in "good" cholesterol versus "bad" cholesterol. Moreover, based upon the disclosure of Sawada et al., it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGF-beta levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption. In addition, an abnormal estrous cycle was observed in the 0.1 mg/kg group, and uterine atrophy and the absence of an estrous cycle occurred for nearly three weeks in the 1 mg/kg group (page 9 of the translation).

While the toxicity observed with toremifene administration, including suppressed weight gain, total cholesterol reduction, and abnormalities of the uterus and estrous cycles, may be acceptable to treat cancer, Sawada et al. do not provide the suggestion or motivation to reach the

present invention, e.g., locally administering a cytostatic dose of a compound of formula (I), e.g., to treat a cardiovascular or vascular indication characterized by a decreased lumen diameter or treat arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy or retinopathy. Thus, Sawada et al. do not teach all the elements of the claims.

Ito et al. is discussed above.

Yang discloses screening methods to identify agents for the treatment of osteoporosis or serum lipid lowering. The method includes the use of eukaryotic cells having a promoter region of a TGF-beta gene that is a raloxifene responsive element (column 7, lines 16-32). The method identifies agents that induce expression from a raloxifene responsive element without inducing deleterious side effects associated with current anti-osteoporosis therapy regimes (abstract). The results in Table 1 show that estradiol, raloxifene and tamoxifen induced expression from TGF-beta2 and TGF-beta3 derived promoters, not TGF-beta1 derived promoters, that were present in human osteosarcoma cells (MG63 cells). The remaining agents were screened on cells with TGF-beta3 derived promoters, i.e., MG63 cells, CHO (Chinese hamster ovary) cells or MCF-7 (breast cancer) cells.

The screening assay disclosed in Yang does not provide a reasonable expectation that an agent that elevates TGF-beta1 levels or a cytostatic dose of a compound of formula (I), would be useful to treat any disease, such as a cardiovascular or vascular indication characterized by a decreased lumen diameter.

Moreover, the Examiner is requested to consider the Rule 132 Declaration enclosed herewith, executed by one of the co-inventors of the present application, Dr. David Grainger. In that Declaration, Dr. Grainger states that prior to the effective filing date of the present application, compounds such as those with structural relatedness to tamoxifen, such as toremifene, were believed to elicit a beneficial effect as a result of their anti-estrogenic activity, and so it was understood that the target for those compounds was the estrogen receptor (paragraph 4 in the Declaration). In this regard, Dr. Grainger points out that all treated rodents in Ito et al. and Sawada et al. were female. He concludes that the use of female rodents in Ito et al and Sawada et al. implies that toremifene was being used because of its anti-estrogenic property and that that conclusion is supported by the generic reference to the class of compounds selected as "non-steroidal anti-estrogens" in the abstract of Ito et al. and the disclosures in both

documents (paragraph 5 in the Declaration). Dr. Grainger avers that there is nothing in either Ito et al. or Sawada et al. that recognizes that certain compounds that are structurally related to tamoxifen have a beneficial effect as a result of their TGF-beta, e.g., TGF-beta1, elevating property, and that this property is unrelated to the anti-estrogenic activity of compounds (paragraph 5 in the Declaration) (paragraph 5 of the Declaration).

In response to the Examiner's assertion that Yang teaches that toremifene is useful for treating osteoporosis because it induces human fetal fibroblasts to secrete TGF-beta in the absence of the estrogen receptor, Dr. Grainger points out that the isoform of TGF-beta secreted from those human fetal fibroblasts was not known and that the observation that toremifene induces TGF-beta secretion from human fetal fibroblasts does not logically lead to the conclusion that toremifene is useful for treating osteoporosis because those cells are not present in individuals with osteoporosis (paragraph 7 in the Declaration). Dr. Grainger also points out that any effect observed with estradiol, raloxifene or tamoxifen treatment in Yang most likely is attributed to estrogen receptor binding of those agents (paragraph 8 in the Declaration).

Dr. Grainger concludes that none of Sawada et al., Ito et al. or Yang provides a reasonable expectation that particular compounds that are structurally related to tamoxifen would have an activity that is not associated with the estrogen receptor but is associated with a therapeutic effect *in vivo* (paragraph 9 in the Declaration). That is because it is not possible to determine the properties of the members of the recited class by understanding the properties of those compounds which also happen to be anti-estrogens and which exert particular properties as a result of that anti-estrogenic activity (paragraph 10 in the Declaration). Moreover, Dr. Grainger states that it was surprising that compounds within the scope of the claims would be useful to inhibit or treat a variety of cardiovascular or vascular indications, since the presence of anti-estrogenic activity in a sub-group of the compounds would not have predicted this (paragraph 11 in the Declaration). Continuing, he states that as of the effective filing date of the present application, estrogen was considered to be unequivocally cardioprotective, since (compared to men) women are relatively protected from cardiovascular disease prior to menopause, when estrogen levels are higher, yet after the menopause have a similar age-corrected risk of cardiovascular disease to men (paragraph 11 in the Declaration). On this basis,

he points out that anti-estrogens would have been expected, if anything, to exacerbate the risk of cardiovascular disease (paragraph 11 in the Declaration).

In response to the Examiner's assertion that in view of the reduction of total cholesterol in female rats after toremifene administration in Sawada et al., one of skill in the art would be motivated to administer toremifene to achieve the expected benefit of lowering total cholesterol in a mammal suffering from atherosclerosis, Dr. Grainger states that the lowering of total cholesterol by a particular agent does not by itself have any bearing on whether that the agent would in any way be beneficial in lowering "bad" cholesterol (that is, LDL cholesterol), much less indicate that the agent would be beneficial in preventing or inhibiting heart disease (paragraph 14 in the Declaration).

Thus, withdrawal of the § 103 rejections over Sawada et al., Ito et al., Yang, and Yang and Frank is respectfully requested.

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231 and 234 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Grainger et al. (WO 94/26303) in view of Chander et al. This rejection is respectfully traversed.

Although WO 94/26303 discloses that tamoxifen and other TGF-beta elevating agents may be useful to treat certain cardiovascular diseases or conditions, as discussed in the Rule 132 Declaration enclosed herewith, it was surprising that compounds within the scope of the claims in the present application would be useful to inhibit or treat a variety of cardiovascular or vascular indications, as they would have been expected to act as anti-estrogens and that would have been expected to exacerbate the risk of cardiovascular disease. Moreover, although certain compounds may be structurally related to tamoxifen, not all of those compounds have a beneficial effect as a result of their TGF-beta, e.g., TGF-beta1, elevating property which property is unrelated to anti-estrogenic activity.

Therefore, withdrawal of the § 103 rejection over Grainger et al. and Chander et al. is respectfully requested.

The Non-Statutory Obviousness-TypeDouble Patenting Rejections

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims

153-173 of co-pending application Serial No. 10/729,056. As neither the present application nor the '056 application has been allowed, no terminal disclaimer is required at this time. Should a terminal disclaimer be required, the Office may request it upon a notice of allowable subject matter in either the present application or the '056 application.

Claims 200, 202-203 and 205-206 were rejected under the judicially created doctrine of obviousness-type double patenting over claim 8 of U.S. Patent No. 6,410,587 in view of Grainger et al. (WO 94/26303). This rejection is respectfully traversed.

Claim 8 in the '587 patent is directed to a therapeutic method for lowering serum cholesterol comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula VI.

In contrast, claim 200 in the present application is directed to a method of increasing the level of TGF-beta in a human identified as being afflicted with a cardiovascular indication characterized by a decreased lumen vessel diameter, comprising administering to the human an effective amount of an agent that directly or indirectly elevates the level of active TGF-beta1 in said human, wherein the agent is a structural analog of tamoxifen or a pharmaceutically acceptable salt thereof.

Claims 173-177, 179-194, 196-200, 202-203, 205-206, 231, and 234 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5,847,007 in view of Chander et al. (Cancer Res., 51:5851 (1991)).

The claims in the '007 patent are directed to a method for preventing atherosclerosis in a mammal at risk therefore, or treating atherosclerosis in a mammal, which method comprises orally administering to the mammal the following: a dose of a therapeutic agent in an amount effective when administered orally to elevate the level of TGF-beta, wherein the increase in TGF-beta inhibits atherosclerotic lesion formation or development in the mammal; and a therapeutic method comprising orally administering to a mammal an amount of a therapeutic agent effective upon oral administration to elevate the level of TGF-beta so as to treat a diseased blood vessel in said mammal, wherein said disease is associated with the diminution in the lumen volume of the diseased vessel, and wherein the therapeutic agent stabilizes atherosclerotic plaque, inhibits lipid accumulation, or inhibits or reduces diminution in vessel lumen diameter in the diseased vessel.

In contrast, claim 173 in the present application includes local administration of a cytostatic dose of a compound of formula (I), claim 182 in the present application includes administering a compound of formula (I) to a diabetic mammal, claim 200 in the present application includes selecting an agent that is structural analog of tamoxifen or a pharmaceutically acceptable salt thereof that directly or indirectly elevates the level of active TGF-beta1 in a human and administering an effective amount of that agent, and claim 231 in the present application is directed to a method for treating arteriosclerosis, silent myocardial infarction, vascular insufficiency in the limbs, peripheral neuropathy, or retinopathy with an effective amount of a compound of formula (I).

Therefore, withdrawal of the nonstatutory obviousness-type double patenting rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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Date August 3, 2009 By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on August 3, 2009.

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